

Papillomas of the breast: factors associated with underestimation

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The distinction between benign and malignant papilloma of the breast through percutaneous needle biopsy can be difficult because of limited samples; the underestimation rate can be up to 25%. The aim of this study is to identify clinical and histological factors associated with underestimation, invasive ductal carcinoma, or ductal in-situ carcinoma (DCIS) of the breast found in surgical specimens from papillary lesions. This may contribute toward selection of patients for a follow-up strategy without the need for surgical excision. From a database of 3563 patients, we identified 85 with intraductal papilloma between 2007 and 2013 who had undergone breast-imaging studies, percutaneous needle biopsy, and surgical resection of the lesion. Central papillomas normally present with a palpable mass, whereas peripheral papillomas generally do not have clinical manifestations (microcalcifications); both central and peripheral papillomas were related to atypical lesions, 13.5 and 15.4%, respectively. Among the 59 cases of central papillomas, there were four cases of underestimation, three DCIS and one invasive ductal carcinoma (6.8%). Among the 26 cases of peripheral papillomas, there was one case of

DCIS (3.8%), with a total underestimation rate of 5.8%; all underestimated lesions measured more than 1 cm. The median size was 11 mm at mammography and 19 mm at ultrasound. Our data suggest that lesions less than 1 cm in size, without atypia and concordant imaging and clinical findings, may not require surgical resection. *European Journal of Cancer Prevention* 27:310–314 Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Papillary lesions of the breast consist of a heterogeneous group that includes benign and malignant lesions (Jacobs *et al.*, 2002; Richter-Ehrenstein *et al.*, 2011; Lu *et al.*, 2012). Once a papillary lesion is diagnosed in percutaneous needle biopsy, the current recommendation is surgical excision, on the basis of the risk of underestimation for carcinoma, which can be up to 25%. The distinction between benign and malignant lesions through percutaneous needle biopsy can be difficult, especially in cases with limited material and with discontinuous fragments (Ueng *et al.*, 2009; Lu *et al.*, 2012; Foley *et al.*, 2015).

Papillary lesions may have many different presentations such as nipple discharge, palpable breast mass, or breast-imaging study finding. Consequently, they can have different image presentations, such as a circumscribed lump, an irregular

lump, or a dilated duct in the retroareolar region (Ohuchi *et al.*, 1984; Ali-Fehmi *et al.*, 2003; Lewis *et al.*, 2006; Ueng *et al.*, 2009; Jagmohan *et al.*, 2013; Foley *et al.*, 2015). The correlation between clinical and imaging findings with the histopathological diagnosis of the surgical specimen is yet to be determined (Ueng *et al.*, 2009).

The most common papillary lesion is the intraductal papilloma, which may be categorized as central or peripheral according to its location in the breast. Apparently, central papillomas, which are commonly single lesions, have a lower chance of association with atypical hyperplasia or ductal carcinoma in-situ than peripheral papillomas, which normally present as multiple lesions (Jacobs *et al.*, 2002). Multiple papillomas have a higher association with atypia and malignancy (32–72%) than central papillomas (0–15%) (Ohuchi *et al.*, 1984; Jagmohan *et al.*, 2013; Foley *et al.*, 2015). The risk of association with cancer, therefore, is higher in peripheral papillomas (~×3 higher) and the peripheral papillomas with atypia the cancer risk becomes seven times higher (Ueng *et al.*, 2009). Papillary carcinoma of the breast is a rare type of breast cancer

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representing only 1–2% of all breast malignancies, and it is an important differential diagnosis in the group of papillary lesions (Ali-Fehmi *et al.*, 2003).

Several authors evaluated the real risk of underestimation after a percutaneous biopsy by comparing the histopathological findings from the biopsies and the surgical specimens. In image-guided core needle biopsies, the underestimation rate ranged from 4.6 to 18% in cases without atypia and from 13 to 92% in papillomas with atypia. These data suggest that papillomas with atypia should be completely excised, whereas papillomas without atypia could be spared from resection in selected cases (Renshaw *et al.*, 2004; Richter-Ehrenstein *et al.*, 2011; Cuneo *et al.*, 2012; Lu *et al.*, 2012; Tatarian *et al.*, 2016).

The aim of our study is to identify the clinical and histological factors associated with invasive or in-situ breast carcinoma found in surgical specimen of patients in a cohort with papillary lesions diagnosed at percutaneous biopsy.

Patients and methods

Patients

We selected 102 patients from a total of 3563 cases with needle biopsies at Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, presenting a histopathological diagnosis of intraductal papilloma between the years 2007 and 2013.

The inclusion criteria were as follows: diagnosis of intraductal papilloma by percutaneous needle biopsy; complete resection of the breast lesion at the Mastology Section of Disciplina de Ginecologia, Departamento de Obstetrícia e Ginecologia, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo; and preoperative imaging study such as mammogram or breast ultrasound. We excluded patients who did not have a diagnosis of intraductal papilloma by percutaneous needle biopsy or who did not undergo preoperative breast-imaging studies. Papillomas associated with atypical ductal hyperplasia at core biopsy were excluded because atypical ductal hyperplasia is a well-established risk factor (Provencher *et al.*, 2012; Ragoth *et al.*, 2016).

The following data were registered: age, central or peripheral localization of the breast lesion, clinical condition, size of the lesion, presence of atypia (lobular intraepithelial neoplasia, ductal atypical hyperplasia), mammography, and ultrasound findings. Two radiologists and two pathologists with extensive expertise in breast lesions reviewed all cases prospectively. All selected cases had the stored material in our tissue bank.

Papillomas were considered underestimated when the histopathological evaluation of the complete resection specimen diagnosed in-situ carcinoma or invasive carcinoma of the breast.

Statistical analysis

After data distribution analysis, we used the Kruskal–Wallis test in nonparametric data to assess possible differences between the three groups (central, peripheral, and underestimated) in terms of age. The Mann–Whitney test was used in nonparametric data to assess possible differences between groups in lesion size and the likelihood ratio test to assess the differences between the three groups studied in clinical findings and breast-imaging findings. We carried out a logistic regression analysis to investigate possible correlations between the variables.

The significance level in all tests was 5% – that is, results with a *P* values of less than 0.05 were considered statistically significant. Multivariate analysis was carried out in all statistically significant variables.

Ethical approval

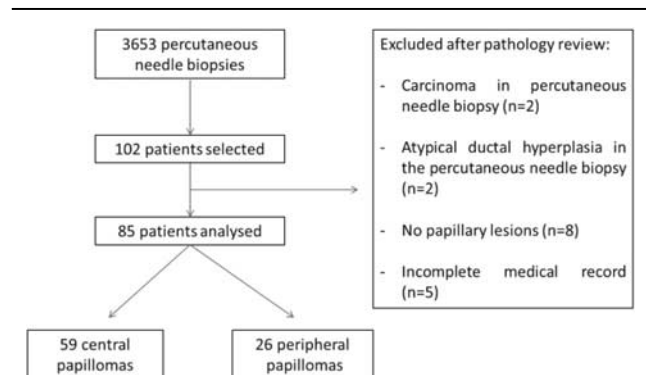
The Ethics Committee of Faculdade de Medicina da Universidade de São Paulo approved this study.

Results

From a database of 3563 patients, we identified 102 with a diagnosis of intraductal papilloma by percutaneous needle biopsy and 85 were included (Fig. 1). Of these, 59 were classified as having central papillomas and 26 were classified as having peripheral papillomas. Among the 59 cases of central papillomas, there were four cases of underestimation (6.8%) (three cases of ductal in-situ carcinoma and one case of invasive ductal carcinoma). Among the 26 cases of peripheral papillomas, there was one case of ductal in-situ carcinoma (3.8% underestimation). In total, five out of 85 cases were underestimated, with a total underestimation rate of 5.8%.

Clinical features, and mammographic and ultrasound characteristics of the patients are shown in Table 1. Central papillomas normally present with clinical symptoms (palpable mass), whereas peripheral papillomas generally do not

Fig. 1



Flowchart showing patients included and excluded in the study.

Table 1 Clinical and radiologic characteristics of the study

Clinical features	Central papilloma (n = 55) [n (%)]	Peripheral papilloma (n = 25) [n (%)]	Underestimated papilloma (n = 5) [n (%)] ^b	P ^a
Age				
N	55	25	5	0.59
Median (range)	49 (29–82)	50 (31–73)	50 (48–79)	
Clinical condition				
Palpable mass	20 (36.3)	1 (4)	1 (20)	0.007
Nipple discharge	10 (18.2)	2 (8)	0 (0)	
Asymptomatic	22 (40.0)	22 (84.6)	4 (80)	
Palpable mass and nipple discharge	3 (5.4)	0 (0)	0 (0)	
Mammography				
Circumscribed mass	14 (25.5)	1 (4)	2 (40)	0.02
Irregular mass	15 (27.3)	2 (8)	1 (20)	
Calcifications	2 (3.6)	12 (48)	1 (20)	
Architectural distortion	1 (1.8)	1 (4)	0	
Focal asymmetries	2 (3.6)	2 (8)	1 (20)	
Normal mammography	12 (21.8)	5 (20)	0	
Not available	9 (16.4)	2 (8)	0	
Ultrasound				
Circumscribed mass	9 (16.4)	1 (4)	0	0.148
Irregular mass	14 (25.5)	8 (32)	2 (40)	
Intraductal image	16 (29.1)	0	0	
Textural change	1 (1.8)	3 (12)	0	
Complex cysts	13 (23.6)	0	2 (40)	
Normal ultrasound	2 (3.6)	10 (40)	0	
Not available	0	3 (12)	1 (20)	
Size (mm)				
Mammography				
N	46	17	5	0.06
Median (range)	16 (4–74)	15 (4–80)	11 (11–20)	
Ultrasound				
N	55	22	4	
Median (range)	12 (4–49)	15 (4–80)	19 (7–29)	

^aCompared the central papilloma with peripheral papilloma.

^bPapillomas were considered underestimated when the histopathological evaluation of the complete resection specimen diagnosed in-situ carcinoma or invasive carcinoma of the breast.

Italic value indicates the Mann–Whitney test.

have clinical manifestations and were found in routine breast-imaging studies (microcalcifications) ($P = 0.007$). The median size at mammography was 11 mm and that at ultrasound was 19 mm; all underestimated lesions measured more than 1 cm (using the largest size).

Both central and peripheral papillomas were related to atypical lesions. After complete resection, we identified atypical lesions in eight (13.5%) central papillomas and four (15.4%) peripheral papillomas. These finds suggest that papillomas are related to proliferative lesions.

The findings of imaging studies, type of biopsy, and pathology diagnosis after complete resection of the underestimated cases are shown in Table 2.

Discussion

Some authors suggest that all papillary lesions should be completely resected because of the technical difficulty of analyzing only part of the lesion acquired in a percutaneous needle biopsy, which may lead to a considerable

likelihood of underestimation and misdiagnose as high as 25% (Jacobs *et al.*, 2002; Ueng *et al.*, 2009; Lu *et al.*, 2012; Foley *et al.*, 2015). In our study, we found an underestimation rate of 5.8%, probably related with the improvement of breast image (better image definition) and biopsy technology (better sampling of the target), resulting in a more accurate diagnosis. Foley *et al.* (2015) performed a multicenter, international, retrospective review of core biopsy-diagnosed breast papillomas and found that atypia on core needle biopsy was significantly associated with a final pathological diagnosis of malignancy (odds ratio = 2.73); in these cases, surgical biopsy is recommended. However, other studies support that cases without atypia or cases in which the lesion was completely removed through percutaneous biopsy did not require surgical resection, claiming that the rate of underestimation is low and related to the presence of atypia in the percutaneous biopsy (Ali-Fehmi *et al.*, 2003; Richter-Ehrenstein *et al.*, 2011; Tatarian *et al.*, 2016).

The evaluation of a patient with a papillary lesion should be careful and very detailed as the clinical, radiological, and pathological findings must be concordant. Ideally, a breast care specialist should perform the evaluation to decrease the risk of underestimation. These patients should be monitored by periodical visits for physical examination, mammography, and breast ultrasound as they have an increased risk of developing breast cancer.

In our study, the total underestimation rate was 5.8 and 6.8% for central papillomas and 3.8% for peripheral papillomas. Atypical cells were found in eight (13.5%) patients with central papillomas and in four (15.4%) patients with peripheral papillomas. Tatarian *et al.* (2016) operated on 75 patients with benign papillomas diagnosed with core needle biopsy and found that 21.3% had atypia in surgical excision; the majority (94.4%, 17/18) of these findings were obtained in the surrounding breast tissue upon excision and not within the sampled papilloma itself. According to Kuzmiak *et al.* (2014), these findings suggest that these patients have more proliferative breasts with an increased lifetime risk of breast cancer compared with the general population.

Compared with the existing literature, we found a lower underestimation rate for peripheral papillomas (32–72%) and a similar underestimation rate for central papillomas (0–15%) (Ohuchi *et al.*, 1984; Lewis *et al.*, 2006; Jagmohan *et al.*, 2013).

The size of the lesions was similar when comparing central papillomas and peripheral papillomas. In the underestimated cases, the size of the lesions in breast ultrasound was higher than the others (the median size of central papillomas was 12 mm, the median size of peripheral papillomas was 15 mm, and the median size of underestimated papillomas was 19 mm), suggesting that the size of the lesion should be taken into consideration when deciding whether to completely resect a papillary

Table 2 Characteristics of the underestimated papillomas^a

Characteristics	Patient nos				
	1	2	3	4	5
Lesion at mammography	Focal asymmetry	Circumscribed mass	Circumscribed mass	Irregular mass	Calcifications
Size (mm)	–	15	20	11	11
Lesion at ultrasound	Irregular mass	Complex cyst	Complex cyst	Irregular mass	Normal
Size (mm)	29	16	22	7	–
Type of biopsy	Core biopsy	Core biopsy	Core biopsy	Core biopsy	VAC
Needle (G)	12	12	12	18	9
Biopsy results	Papilloma	Sclerosing papilloma	Sclerosing papilloma	Papilloma And LIN	Papilloma
Final pathology	DCIS	DCIS	DCIS	IDC	DCIS
Presence of ADH in surgical specimen	Yes	Yes	Yes	No	Yes
Presence of LIN in surgical specimen	No	Yes	Yes	No	Yes
Treatment	Wide lesion excision	Mastectomy + SNB	Mastectomy + SNB	Lumpectomy + SNB	Wide lesion excision
Surgical specimen findings	No residual disease	Microinvasive ductal carcinoma, hormone receptor positive	DCIS	Low grade IDC, hormone receptor positive	Nuclear grade 2 DCIS
Adjuvancy	Tamoxifen	Tamoxifen	Tamoxifen	Radiotherapy + anastrozole	Radiotherapy + anastrozole

ADH, atypical ductal hyperplasia; DCIS, ductal in-situ carcinoma; IDC, invasive ductal carcinoma; LIN, lobular intraepithelial neoplasia; SNB, Sentinel node biopsy; VAC, Vacuum-assisted Core needle biopsy.

^aPapillomas were considered underestimated when the histopathological evaluation of the complete resection specimen diagnosed in-situ carcinoma or invasive carcinoma of the breast.

lesion or not; all underestimated lesions measured more than 1 cm (using the largest size). Kuzmiak *et al.* (2014) showed that papillary lesions more than 1 cm in size presented higher rates of underestimation (11%) compared with lesions less than 1 cm in size (1%).

Swapp *et al.* (2013) followed 100 patients with central papillomas, without atypia, completely removed by percutaneous biopsy for 36 months. There were no suspicious findings during follow-up. Mosier *et al.* (2013) followed 86 patients for 2 years with papillomas with less than 1.5 cm in size without atypia, also completely removed in the percutaneous biopsy. No suspicious lesions were diagnosed during follow-up. Yi *et al.* (2013) followed 103 patients with papillomas without atypia for 33 months and did not find suspicious alterations during follow-up. These studies show that papillomas without atypia, completely removed in the percutaneous biopsy, do not require additional surgical resection and patients can be safely followed by physical examination and breast-imaging studies. Some authors go a little further and suggest that patients with papillary lesions without atypia with a small residual lesion may not need surgical resection.

In terms of the limitations of our study, because of a small number of patients, a multivariate analysis was unfeasible and there were some missing data because of loss to follow-up. However, evaluation by the same pathologist and radiologist enabled uniformity in the interpretation and examination reports.

Conclusion

Patients with lesions smaller than 1 cm in size and without atypia have a low risk of underestimation. Our

results suggest that small (< 1 cm) intraductal papillomas, without atypia, completely removed in percutaneous needle biopsy and with concordant clinical and radiological findings, can be managed without the need for surgical resection. Further studies are necessary to safely determine the best way to follow-up patients who can be spared a complete surgical resection of a papillary lesion.

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Conflicts of interest

There are no conflicts of interest.

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